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HLA-G and NK Receptor Are Expressed in Psoriatic Skin

A Possible Pathway for Regulating Infiltrating T Cells?

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Recent data have suggested that in psoriasis, the T-infiltrating cells could be submitted to regulatory pathways, possibly through natural killer receptors. HLA-G binds to different natural killer receptors and is able to inhibit T-cell functions. Because this molecule is induced by interferon-γ, a major cytokine in psoriasis, we asked whether HLA-G and its receptor might be expressed in this disease. Specific RNAs for HLA-G1 and HLA-G5 were consistently found in lesional skin specimens, soluble HLA-G5 transcripts being found only in psoriasis. HLA-G protein was found in all psoriatic sections, but never in normal skin controls. Double labeling demonstrated that HLA-G-positive cells were CD68$^+$, CD11c$^+$ macrophages. The NKR ILT2 was also present in psoriatic skin, the T CD4$^+$-infiltrating cells expressing indeed ILT2. The demonstration of HLA-G and ILT2 expression in psoriatic skin suggests that this pathway may act as an inhibitory feed back aimed to down-regulate the deleterious effects of T-cell infiltrate in this disease. *(Am J Pathol 2001, 159:71–77)*

Psoriasis is a chronic disabling skin disease that affects two percent of the population and is therefore responsible for a significant morbidity.[1] Although cutaneous lesions are characterized by an intense hyperproliferation of epidermal keratinocytes, several data have demonstrated that this disease was mediated by T cells. Indeed, in psoriatic skin, T lymphocytes are always present at the site of the disease and their infiltration precedes the epidermal changes.[2] Supernatants of T-cell clones derived from psoriatic skin lesions are able to induce hyperproliferation of the epidermis.[3] In accordance, induction and maintenance of the psoriatic phenotype in human biopsies transplanted on SCID mice was dependent on co-injection of T lymphocytes derived from the lesions.[4,5] Of note, only CD4$^+$ but not CD8$^+$ T cells were able to lead to the induction of psoriatic phenotype.[6] In patients with psoriasis, treatments targeting T cells such as cyclosporin, lymphocyte-selective toxin, or soluble chimeric protein CTLA4Ig are efficient in clearing skin lesions.[7–9] Finally, several authors have shown that the infiltrating T lymphocytes expressed the Th1 cytokine interferon-γ (IFN-γ).[10,11] Altogether, these data have led to a general agreement about the major role of T cells, rather than epidermal cells, in the pathogenesis of psoriasis.

Besides these data, recent studies have emphasized the potential role of natural killer receptors (NKRs) in psoriasis. These receptors were indeed found in human psoriatic lesions[6] as well as in an animal model,[12] but not in normal skin.[6] These NKRs recognize various class I alleles, such linking being able to down-regulate several lymphocytic pathways. NKR binding may therefore play an important role in the regulation of the disease pathways. HLA-G is a nonclassical class I MHC molecule, whose expression is restricted to a few tissues such as cytotrophoblasts and thymic epithelial cells.[13] HLA-G interacts with different NKRs such as ILT2[14,15] KIR2DL4,[16] and p49[17] and is able to inhibit both natural killer (NK)[18] and T-cell cytotoxicity as well as to inhibit T-cell proliferation.[19,20] There are six isoforms for this molecule: four are membrane-bound (HLA-G1, -G2, -G3, and -G4) and two are soluble (HLA-G5 and -G6);[13] their expression being enhanced by IFN-γ.[21] HLA-G has been shown to play a crucial role in the protection of the fetus toward the mother's immune cells.[22] In addition, it has also been recently suggested that the expression of HLA-G in melanoma may participate in the mechanisms of escape of the tumor from the immune surveillance of the host.[23,24] HLA-G seems therefore to be able to down-regulate several lymphoid reactions in various situations. Because psoriasis is a disease characterized by the secretion of cytokines also able to up-regulate HLA-G, and because psoriatic infiltrating cells express NKR receptors, we

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asked whether HLA-G and its receptor might be expressed in this disease.

Materials and Methods

Source of Specimens

To be eligible for inclusion in this study, patients had to 1) display typical lesions of chronic plaque type psoriasis, 2) did not receive any systemic or local therapy for at least 14 days before biopsy, and 3) give informed consent. Control skin was obtained from healthy females who underwent breast reduction surgery. The obtained specimens were cut into two parts. One part was snap-frozen in liquid nitrogen and used for reverse transcription-polymerase chain reaction (RT-PCR) whereas the other was placed in OCT for immunohistochemical analysis.

RT-PCR

RNA isolation followed by RT-PCR was performed according to the manufacturer's recommendations. Briefly, the skin biopsies stored at −80°C were put in RNA Now reagent (Biogentex, Seabrook, TX) and homogenized using ultraturrax (IKA Labortechnic, Staufen, Germany) according to the manufacturer's recommendations. The quality of RNA was checked by electrophoresis on 1.5% agarose gel. Five μg of mRNA was reverse-transcripted into cDNA using oligo (dT)12-18 primer (Life Technologies, Cergy Fontoise, France), and Moloney murine leukemia virus reverse transcriptase (Life Technologies) at 42°C for 1 hour. The cDNA obtained was used for PCR. Amplifications were performed as previously described using the primers G.257 (5′-GGA AGA GGA GAC ACG GAA CA) and G3U 55′-(GGC TGG TCT CTG CAC AAA GAG A). These primers amplify all HLA-G isoforms. Specific amplification of the soluble HLA-G5 transcript was performed using primers G.526 (5′-CCA ATG TGG CTG AAC AAA GG) and G.i4b (5′-AAC GGA GAA GGT GAG GG) primers. The PCR was conducted for 35 cycles, consisting of 1 minute at 90°C, 90 seconds at 65°C (61°C for G5), and 2 minutes at 72°C. PCR products were run on 1.5% agarose gels. Co-amplification of β-actin cDNA was performed in each sample, using the β-actin amplimer set (Life Technologies) for 16 cycles to assess that equal amounts of material were loaded in each well.

Radioactive Hybridization of PCR Products

PCR products were then transferred by alkaline blotting onto nylon membranes (Hybond-N+, Amersham) and hybridized with a (γ-^{32}P)ATP end-labeled oligonucleotide probe. The GR probe that recognizes all HLA-G-isoforms has the following sequence: 5′-GGT CTG CAG GTT CAT TCT GTC. The HLA-G5-specific probe sequence is: 5′-GAG GCA TCA TGT CTG TTA GG. The bands were quantified by densitometry.

Immunohistochemistry

Four-μm cryostat sections were taken from frozen specimens, dehydrated in acetone at −20° for 10 minutes, and then air-dried. The DAKO EnVision+ System, peroxidase (amino ethyl carbazol) (DAKO, Carpinteria, CA) was used. Briefly, after rinsing sections in phosphate-buffered saline with 0.1% saponin, endogenous peroxidases were inhibited using H_2O_2, and then the samples were incubated for 1 hour at room temperature with the specific or irrelevant antibodies. The sections were then put in a solution containing a peroxidase-labeled polymer conjugated to a goat anti-mouse immunoglobulin for 30 minutes. The diaminobenzidine plus substrate-chromogen was finally used for revealing the antibody fixation. The antibodies used were: 87G and O1G (both specific for HLA-G1 and G5); 16G1 (specific for the soluble G5 isoform) (these antibodies being kindly provided by Dan Geraghty, Fred Hutchinson Cancer Research Center, Seattle, WA); 4H84, recognizing denatured HLA-G isoforms (kindly provided by Dr. M. Mc Master, San Francisco, CA); anti-ILT2 that recognizes a NKR involved in HLA-G binding (kindly provided by Dr. Marco Colonna, Basel, Switzerland); w6/32 (anti-MHC class I) (Sigma Chemical Co., St. Louis, MO); CD3, CD14, and a mouse-IgG2a as control (Sigma).

Double Labeling

To assess which cells were expressing HLA-G and ILT2, double-labeling experiments were used with 87G and anti-CD68; 87G and anti-CD11c, anti-ILT2, anti-CD3, anti-CD4, and anti-CD8. These were performed follows. After incubation with normal goat serum, lesional sections were incubated with mouse monoclonal antibody 87G for 60 minutes, rinsed, and incubated with goat anti-mouse IgG conjugated with Texas Red. After rinsing, sections were incubated for 30 minutes with fluorescein isothiocyanate (FITC)-conjugated CD68 or FITC-conjugated CD11c antibodies. Controls consisted in same studies with replacement of 87G with IgG. In the same way, double immunostaining with anti-ILT2 and FITC-conjugated anti-CD3, anti-CD4, or anti-CD8 were performed to evaluate the presence of T cells expressing the ILT2 receptor. Controls consisted in same studies with replacement of anti-ILT2 with IgG. The sections were examined using confocal laser microscopy.

Results

Identification of Alternatively Spliced HLA-G mRNA Transcripts in Psoriatic and Healthy Skin

The amounts of HLA-G mRNA obtained from six psoriatic plaque specimens and four healthy skin controls were analyzed by RT-PCR. HLA-G isoforms were consistently found in all psoriatic specimens, but in only two of the four normal control skin biopsies (Figure 1). With the exception of one specimen (case 3), only the bands corresponding to the HLA-G1 and HLA-G5 isoforms were

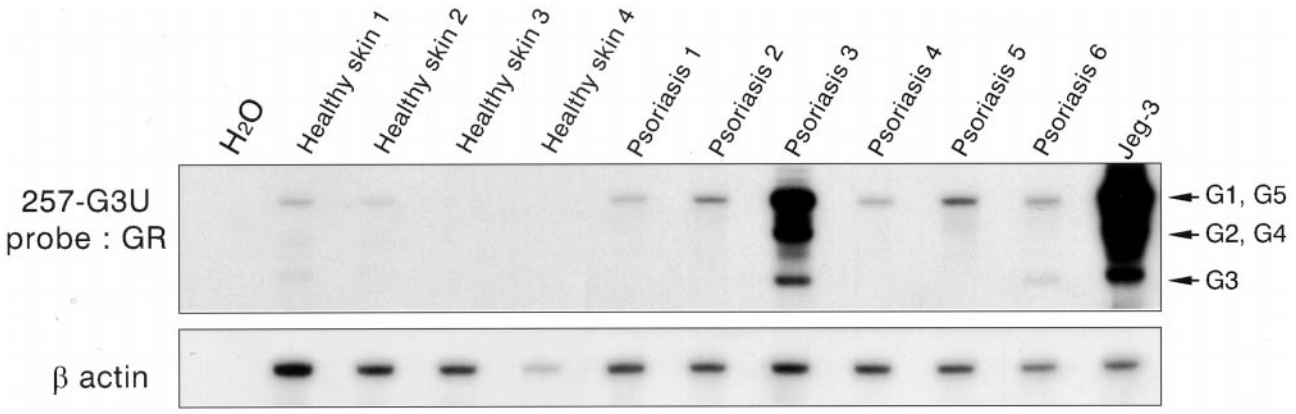

Figure 1. Top: RT-PCR analysis with HLA-G primers followed by consensus probe showing constant detection of HLA-G mRNA isoforms in psoriatic specimens whereas only two of four specimens of control skin disclosed HLA-G RNA. Jeg 3 is a choriocarcinoma cell line known to express high levels of HLA-G mRNA. **Bottom:** β-actin levels amplified in same specimens.

found in psoriatic lesions. Patient 3 had a severe resistant disease, with psoriatic arthritis. Finally, the level of the HLA-G1/G5 transcripts appeared more intense in the psoriatic specimens compared to normal controls.

Identification of the Soluble HLA-G5 mRNA Transcripts in Psoriatic and Healthy Skin

The soluble isoform HLA-G5 was studied in the same specimens using primers and probe that are specific for this isoform. A band corresponding to HLA-G5 was demonstrated in three of six psoriatic specimens whereas it was constantly absent from normal skin (Figure 2).

HLA-G Protein Is Expressed in the Skin Lesions

When analyzing nine psoriatic biopsies by immunohistochemistry, a labeling of cells within the papillary dermis was consistently found using the specific HLA-G antibodies 87G and O1G (Figures 3 and 4). The numbers of HLA-G-positive cells was however variable, being very dense in some cases (Figure 4). In only two cases were the stained cells not only within the papillary dermis but also in cells of the epidermis (Figures 4B and 6A). Using 16G1, an antibody that recognizes only the soluble HLA-G5 isoform, positive cells were also found in papillary dermis (Figure 3). In contrast, normal skin never expressed HLA-G (Figure 5). To determine which types of infiltrating cells were expressing HLA-G, serial sections labeled with 87G antibodies, CD3 and CD14 antibodies were performed. The HLA-G-positive cells never co-localized with T lymphocytes, but were rather close to the $CD14^+$ cell distribution (Figure 3).

The HLA-G-Positive Cells Are $CD68^+$ and $CD11c^+$ Macrophages

In view of the above-detailed serial section analysis, we performed double labeling with the HLA-G antibody 87G and anti-CD68 and anti-CD11c antibodies that recognize macrophages. Nearly all HLA-G-positive cells were also labeled with CD68 and CD11c (Figures 6 and 7), demonstrating that macrophages were the source for HLA-G in these specimens.

The KIR Receptor ILT2 Is Present on T $CD4^+$ Infiltrating Cells in Psoriasis

Immunohistochemistry realized on psoriatic sections incubated with anti-ILT2 demonstrated the labeling of a dense infiltrate in the superficial dermis (Figure 4). In contrast, almost no positive cells were found in the dermis of normal skin (Figure 5). Immunohistochemistry with

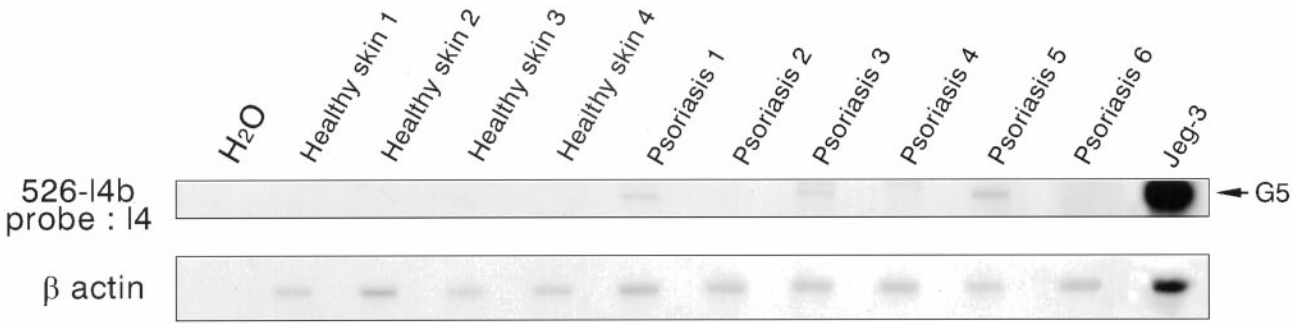

Figure 2. RT-PCR analysis with HLA-G5-soluble isoform primers followed by hybridization with specific G5 probe demonstrating detection of HLA-G5 transcript in three of six psoriatic biopsies (psoriasis 1, 3, and 5) but never in the four control skin biopsies.

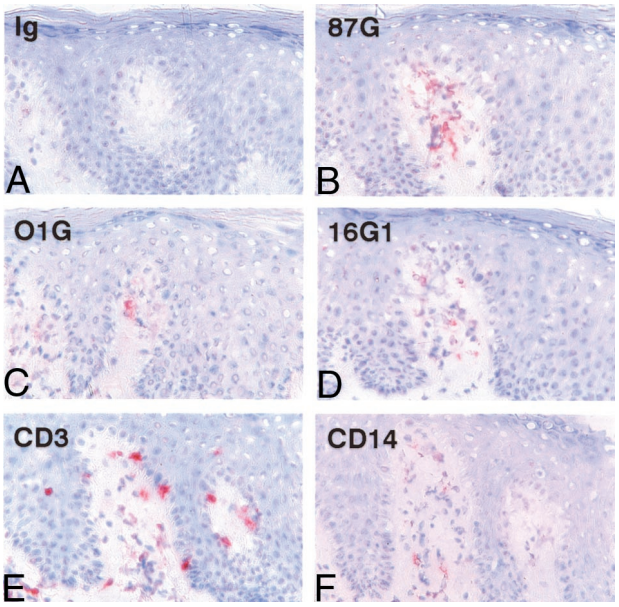

Figure 3. Immunohistochemistry of psoriatic skin sections with antibodies recognizing HLA-G. **A:** Labeling of psoriatic skin with irrelevant antibodies (IgG). **B:** Labeling of psoriatic skin with 87G, an antibody specific for HLA-G1 and HLA-G5 isoforms. **C:** Labeling of psoriatic skin with O1G, another antibody with same reactivities as 87G. **D:** Immunohistochemistry with 16G1, an antibody specific for the HLA-G5 soluble isoform. **E** and **F:** Labeling of same biopsy sections with CD3 and CD14 antibodies, respectively. HLA-G-positive cells are present within papillary dermis as shown in **B**, **C**, and **D**. Soluble isoform-producing cells are demonstrated with 16G1 antibodies (**D**). Finally, serial sections suggest co-localization of HLA-G-positive cells with macrophages (CD14) rather than with T cells.

anti-CD3 and anti-ILT2 antibodies showed afterward the presence of several double-positive cells in papillary dermis (Figure 8). In addition, double immunofluorescence with anti-ILT2 and FITC-labeled anti-CD4 or anti-CD8 antibodies showed that the T cells expressing ILT2 in psoriasis were only T $CD4^+$ cells. CD8-positive cells were not labeled with ILT2.

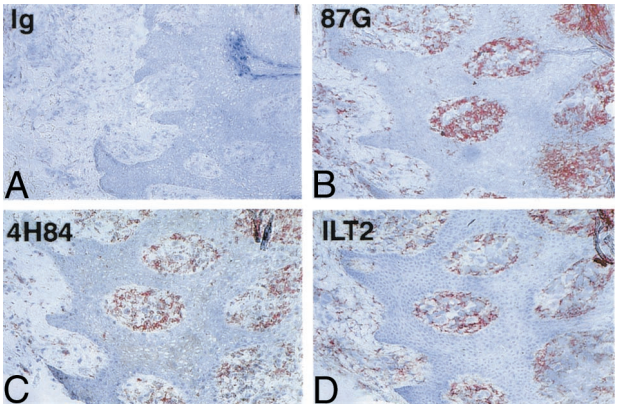

Figure 4. Immunohistochemistry of psoriatic skin sections from a different patient than that in Figure 3. **A:** Labeling of psoriatic skin with IgG. **B:** Labeling of psoriatic skin with 87G. **C:** Labeling of psoriatic skin with 4H84, an antibody recognizing all HLA-G isoforms. **D:** Labeling of psoriatic skin with anti-ILT2. Presence of a high number of cells expressing HLA-G within dermal papillae of psoriasis (**B** and **C**). Of note, HLA-G-positive cells seem also to appear within keratinocytes adjacent to a dermal papilla in **B**. Finally, cells expressing ILT2, a known receptor for HLA-G, are also found within dermal papillae (**D**).

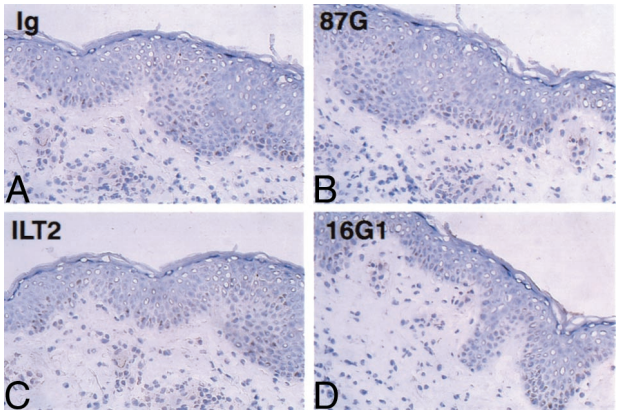

Figure 5. Immunohistochemistry of normal skin obtained from breast reduction surgery and labeled with antibodies recognizing HLA-G and its receptor. **A:** Labeling of normal skin with IgG. **B:** Labeling of normal skin with 87G. **C:** Labeling of normal skin with anti-ILT2. **D:** Labeling of normal skin with 16G1. These sections show that there are no HLA-G-positive cells or ILT2-positive cells within normal skin.

Discussion

The central role of T lymphocytes in the pathogenesis of psoriasis has now been demonstrated. However, it has recently been shown that the T-infiltrating cells functions could be submitted to regulatory pathways. Indeed, the injection of activated mononuclear cells derived from psoriatic patient biopsies within allogeneic normal skin led to the development of a psoriatic phenotype rather than to a graft-*versus*-host disease.[12] In addition, although cytotoxic granules TiA1 are found in CD8 cells from psoriatic epidermis, a cytopathogenic effect was never found in the adjacent keratinocytes.[25] In addition, NKRs have been identified on infiltrating cells in psoriatic lesions.[6] Because the inhibiting functions of HLA-G on T cells have recently been shown and because the expression of this molecule is induced by IFN-γ, a cytokine constantly found in psoriasis;[9,10] we asked whether HLA-G may be implicated in the control of this disease. Our results demonstrate that HLA-G was present at lesional sites of psoriasis. Indeed, specific RNAs for membrane bound and soluble isoforms HLA-G1 and HLA-G5 were consistently found in lesional skin specimens, their levels seeming to be higher than that of controls. In addition, soluble HLA-G5 transcripts were only found in psoriasis. Overall, HLA-G protein expression was found in all psoriatic sections examined, but never in sections from normal skin. This expression was demonstrated by three different monoclonal antibodies. The expression of the soluble protein HLA-G5 was also shown at the same sites.[26] Our results are slightly different from those of Ulbrecht and colleagues[27] who have suggested that the levels of HLA-G transcripts may be decreased in psoriasis. However, only two specimens of normal skin were analyzed by RT-PCR, the levels of these two specimens being very different, making a clear-cut conclusion difficult to assess. In addition, analysis of soluble isoforms and protein analysis was not done in this study.

The expression of HLA-G was always found within lining infiltrating cells in the papillary dermis. In psoriatic lesions, previous studies have shown the presence of a

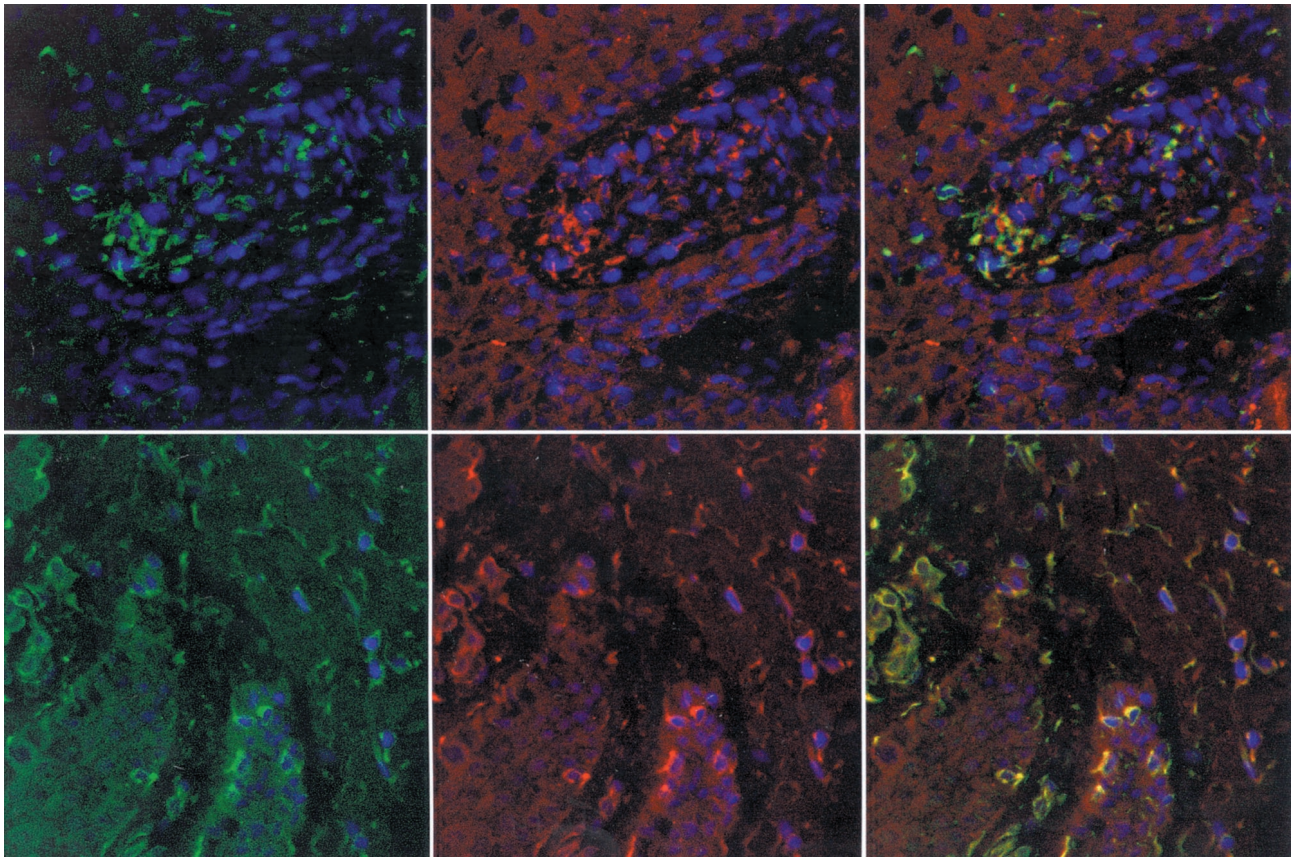

Figure 6. Double-immunofluorescence analysis of psoriatic sections from two patients (cases A and B) incubated with 87G, an antibody specific for HLA-G, followed by Texas Red-conjugated anti-mouse antibodies, then incubated with FITC-conjugated anti-CD68 antibodies (see Materials and Methods) In green (**right**, **top** and **bottom**): CD68-positive cells. In red (**middle**, **top** and **bottom**): HLA-G-positive cells in dermis and to a lower degree in infiltrating cells of the epidermis. In yellow (**right**, **top** and **bottom**): double-positive CD68 and 87G cells in dermis and to a lower degree in epidermal infiltrate.

subset of spindle-shaped macrophages lining below the dermal-epidermal junction.[28,29] This distribution is similar to the HLA-G$^+$ cells observed in this study. Because the spindle-shaped psoriatic macrophages express CD11c$^+$ and CD68$^+$, double-labeling experiments disclosed that the HLA-G$^+$ cells were indeed CD68$^+$ and CD11c$^+$ macrophages. These cells are derived from the monocyte-macrophage lineage, known to be able to express HLA-G in certain circumstances, particularly, when incubated with IFN-γ.[21,30] Therefore, it is tempting to hypothesize that the psoriatic macrophages expressed HLA-G on stimulation by IFN-γ secreted by infiltrating T cells. Finally, in only two cases were HLA-G$^+$ cells also found in the epidermis. However, these cells were either infiltrating cells as these were grouped within isolated small foci close to the dermal labeled infiltrate (Figure 6) or corresponded to few keratinocytes (Figure 4B). In this view, this presence may correspond to the diffusion of soluble

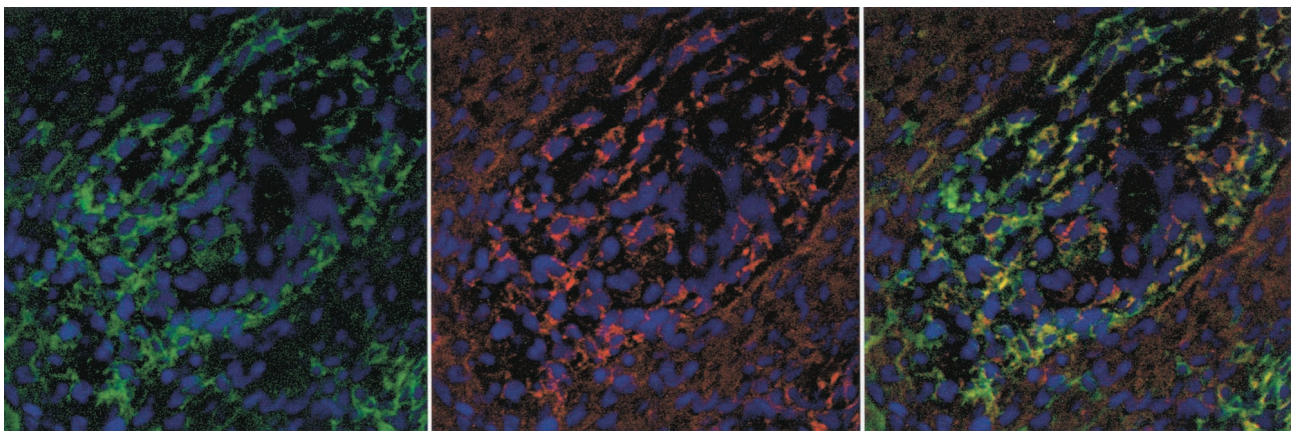

Figure 7. Double immunofluorescence of psoriatic sections with anti-CD11c (green cells, **left**) and 87G (red cells, **middle**), showing double-positive cells (yellow, **right**) in papillary dermis.

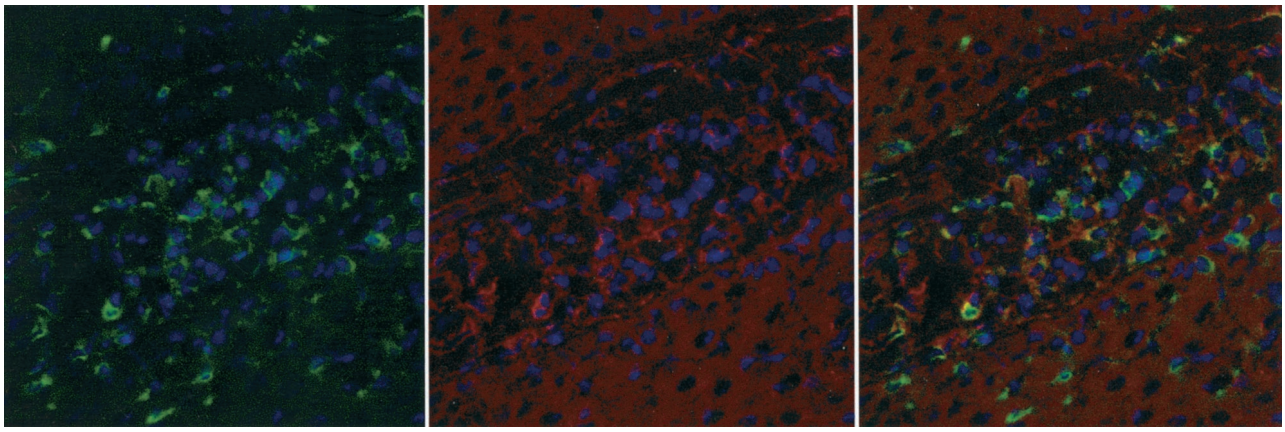

Figure 8. Double staining of psoriatic sections with anti-ILT2, an antibody specific for a receptor able to recognize HLA-G and anti-CD3 (see Materials and Methods). Green T cells are seen at **left** in dermis and to a lower degree in epidermis. Red ILT2-positive cells are seen at **middle**, in the dermis. Double-positive yellow or orange cells are seen at **right** in the dermis.

HLA-G as it was found only closely to dermal HLA-G-producing cells (Figure 4B). In contrast, this presence may also theoretically have resulted from IFN-γ-induced secretion by keratinocytes because these cells in culture may express HLA-G when stimulated with this cytokine (S Aratingi, personal communication). However, this hypothesis is difficult to admit because expression of HLA-G in keratinocytes was found in only one biopsy suggesting that the *in vitro* results do not correlate with *in vivo* results.

HLA-G is a nonclassical MHC molecule able to induce tolerance. Indeed, the transfection of this molecule in cells sensitive to polyclonal NK lysis allows the inhibition of cytolysis.[18] In the same way, trophoblasts expressing HLA-G inhibit decidual NK lysis.[31] These data strongly suggest that the expression of this molecule by the cytotrophoblasts is one of the major tools for the establishment of tolerance of the fetus during pregnancy.[22] More recent studies have shown that HLA-G transcripts and proteins may be found in some melanoma biopsies.[23,24,32] Here too, the transfection of HLA-G in a melanoma cell line that did not express this molecule inhibited *in vitro* T-cell and NK-cell cytotoxicity.[23,32] Other experiments have shown that HLA-G was able to inhibit the allogeneic proliferative T-cell response.[19,20] This inhibition is mediated by the binding of HLA-G to various inhibitory NKRs such as ILT2, ILT4, p49, and KIR2DL4.[14–17] NKRs, originally characterized on NK cells can also be expressed on T-cell subsets. The presence of ILT2 in T $CD4^+$ psoriatic cells found here suggest that pathogenic T cells in this disease can be regulated via the HLA-G pathway. Interestingly, in a very recent study done in an animal model for psoriasis, other NKRs such as CD94, CD158a, CD158b, and NKB1 were found in dermal and epidermal infiltrating T cells;[12] the ratio of cells expressing NKRs being higher than the one expected from peripheral blood findings.[12] These receptors were found in human psoriatic skin lesions, but not in normal skin.[6] The authors proposed that in psoriasis, T cells expressing NKR could be viewed as an early warning back-up system.[12,33] Of note, Fournel and colleagues[34] have recently shown that soluble HLA-G was able to trigger apoptosis of activated CD8 cells, but not resting CD8 cells. $CD8^+$ cytotoxic cells are constantly present in psoriatic epidermis.[25] Despite the presence of these cells, no evidence of cytopathic effects on adjacent keratinocytes is found in psoriasis suggesting that suppressor signals may be implicated.[12] The soluble HLA-G molecule, that we identified in psoriasis, could therefore constitute at least one of the negative pathways that inhibit T-infiltrating cells. This action may target $CD4^+$ cells as suggested in this study, but possibly also $CD8^+$ cells, since a recent work demonstrated that newer antibodies, not yet available, detected ILT2-positive T cells that appeared previously negative with the classical antibodies that we used here.[35] In view of all these findings, the above demonstration of HLA-G and ILT2 expression in psoriasis suggests that this pathway may act as an inhibitory feedback aimed to down-regulate the deleterious effects of initial T-cell infiltrate in this disease. Future analysis, such as functional studies in animal models, will be needed to ultimately assess the role of HLA-G in psoriasis.

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References

1. Greaves MW, Weinstein GD: Treatment of psoriasis. N Engl J Med 1995, 332:581–588
2. Christophers E, Mrowietz U: The inflammatory infiltrate in psoriasis. Clin Dermatol 1995, 13:131–135
3. Strange P, Cooper KD, Hansen ER, Fisher G, Larsen JK, Fox D, Krag C, Voorhees JJ, Baadsgaard O: T-lymphocyte clones initiated from

lesional psoriatic skin release growth factors that induce keratinocyte proliferation. J Invest Dermatol 1993, 101:695–700
4. Gilhar A, David M, Ullmann Y, Berkutski T, Kalish RS: T-lymphocyte dependence of psoriatic pathology in human psoriatic skin grafted to SCID mice. J Invest Dermatol 1997, 109:283–288
5. Wrone-Smith T, Nickoloff BJ: Dermal injection of immunocytes induces psoriasis. J Clin Invest 1996, 98:1878–1887
6. Nickoloff BJ, Wrone-Smith T: Injection of pre-psoriatic skin with CD4+ T cells induces psoriasis. Am J Pathol 1999, 155:145–158
7. Griffiths CE, Powels A, Leonard J, Fry L, Baker BS, Valdimarsson H: Clearance of psoriasis with low dose cyclosporin. Br Med J 1986, 293:731–732
8. Gottlieb SL, Gilleaudeau P, Johnson R, Estes L, Woodworth TG, Gottlieb AB, Krueger JG: Response of psoriasis to a lymphocyte-selective toxin (DAB_{389}IL-2) suggests a primary immune, but not keratinocyte, pathogenic basis. Nat Med 1995, 1:442–447
9. Abrams JR, Lebwohl MG, Guzzo CA, Jegasothy BV, Goldfarb MT, Goffe BS, Menter A, Lowe NJ, Krueger G, Brown MJ, Weiner RS, Birkhofer MJ, Warner GL, Berry KK, Linsley PS, Krueger JG, Ochs HD, Kelley SL, Kang S: CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. J Clin Invest 1999, 103:1243–1252
10. Schlaak JF, Buslau M, Jocum W, Hermann E, Girndt M, Gallati H, Meyer zum Buschenfelde KH, Fleischer B: T cells involved in psoriasis vulgaris belong to the Th1 subset. J Invest Dermatol 1994, 102:145–149
11. Vogel U, Denecke B, Troyanovsky SM, Leube RE, Bottger EC: Transcriptional activation of psoriasis-associated cytokeratin 17 by interferon-γ. Analysis of interferon-γ activation sites. Eur J Biochem 1995, 227:143–149
12. Nickoloff BJ, Wrone-Smith T, Bonish B, Porcelli S: Response of murine and normal human skin to injection of allogeneic blood derived psoriatic immunocytes. Arch Dermatol 1999, 135:546–552
13. Carosella ED, Rouas-Freiss N, Paul P, Dausset J: HLA-G: a tolerance molecule from the major histocompatibility complex. Immunol Today 1999, 20:60–62
14. Colonna M, Navarro F, Bellon T, Llano M, Garcia P, Samaridis J, Angman L, Cella M, Lopez-Botet M: A common inhibitory receptor for major histocompatibility complex class I molecules on human lymphoid and myelomonocytoid cells. J Exp Med 1997, 186:1809–1818
15. Cosman D, Fanger N, Borges L, Kubin M, Chin W, Peterson L, Hsu ML: A novel immunoglobulin superfamily receptor for cellular and viral MHC class I molecules. Immunity 1997, 7:273–282
16. Rajagopalan S, Long EO: A human histocompatibility leucocyte antigen (HLA)-G-specific receptor expressed on all natural killer cells. J Exp Med 1999, 189:1093–1099
17. Ponte M, Cantoni C, Biassoni R, Radori-Cappai A, Bentivoglio G, Vitale C, Bertone S, Moretta A, Moretta L, Mingari MC: Inhibitory receptors sensing HLA-G1 molecules in pregnancy: decidua-associated natural killer cells express LIR-1 and CD94/NKG2A and acquire p49, an HLA-G1-specific receptor. Proc Natl Acad Sci USA 1999, 96:5674–5679
18. Rouas-Freiss N, Marchal R, Kieszenbaum M, Dausset J, Carosella ED: The α domain of HLA-G1 and HLA-G2 inhibits cytotoxicity induced by natural killer cells: is HLA-G the public ligand for natural killer inhibitory receptors? Proc Natl Acad Sci USA 1997, 94:5249–5254
19. Riteau B, Menier C, Khalil-Daher I, Dausset J, Rouas-Freiss N, Carosella ED: HLA-G inhibits the allogeneic proliferative response. J Reprod Immunol 1999, 43:203–211
20. Le Gal FA, Riteau B, Sedlik C, Khalil-Daher I, Menier C, Dausset J, Guillet JG, Carosella ED, Rouas-Freiss N: HLA-G mediated-inhibition of antigen-specific cytotoxic T lymphocytes. Int Immunity 1999, 11: 101–106
21. Yang Y, Chu W, Geraghty DE, Hunt JS: Expression of HLA-G in human mononuclear phagocytes and selective induction by IFN-γ. J Immunol 1996, 156:4224–4231
22. Yokoyama YM: The mother-child union: the case of missing self and protection of the fetus. Proc Natl Acad Sci USA 1997, 94:5998–6000
23. Paul P, Rouas-Freiss N, Khalil-Daher I, Moreau P, Riteau B, le Gal FA, Avirl MF, Dausset J, Guillet JG, Carosella E: HLA-G expression in melanoma: a way for tumor cells to escape from immunosurveillance. Proc Natl Acad Sci USA 1998, 95:4510–4515
24. Wagner SN, Rebmann V, Willers CP, Grosse-Wilde H, Goos M: Expression analysis of classic and non-classic HLA molecules before interferon alfa-2b treatment of melanoma. Lancet 2000, 356:220–221
25. Austin LM, Coven TR, Bhardwaj N, Steinman R, Krueger JG: Intraepidermal lymphocytes in psoriatic lymphocytes are activated GMP-17 (TIA 1)+CD8+CD3+ CTLs as determined by phenotypic analysis. J Cutan Pathol 1998, 25:78–88
26. Lee N, Malacko AR, Ishitani A, Chen M-C, Bajorath J, Marquart H, Geraghty DE: The membrane-bound and soluble forms of HLA-G bind identical sets of endogenous peptides but differ with respect to TAP association. Immunity 1995, 3:591–600
27. Ulbrecht M, Rehberger B, Strobel I, Messer G, Kind P, Degitz K, Bieber T, Weiss EH: HLA-G: expression in human keratinocytes in vitro and in human skin in vivo. Eur J Immunol 1994, 24:176–180
28. Van den Oord JJ, de Wolf-Peeters C: Epithelium lining macrophages in psoriasis. Br J Dermatol 1994, 130:589–594
29. Boehncke WH, Wortmann S, Kaufman R, Mielke V, Sterry W: A subset of macrophages located along the basement membrane (lining cells) is a characteristic histopathological feature of psoriasis. Am J Dermatopathol 1995, 17:139–144
30. Lefebvre S, Moreau P, Guiard V, Ibrahim EC, Adrian-Cabestre F, Menier C, Dausset J, Carosella ED, Paul P: Molecular mechanisms controlling constitutive and IFN inducible HLA-G expression in various cell types. J Reprod Immunol 1999, 43:213–224
31. Rouas-Freiss N, Marchal R, Menier C, Dausset J, Carosella ED: Direct evidence to support the role of HLA-G in protecting the fetus from maternal uterine natural killer cytolysis. Proc Natl Acad Sci USA 1997, 94:11520–11525
32. Paul P, Cabestre FA, Le Gal FA, Khalil-Daher I, Le Danff C, Schmid M, Mercier S, Avril MF, Dausset J, Guillet JG, Carosella ED: Heterogeneity of HLA-G gene transcription and protein expression in malignant melanoma biopsies. Cancer Res 1999, 59:1954–1960
33. Nickoloff BJ: Skin innate immune system in psoriasis: friend or foe? J Clin Invest 1999, 104:1161–1164
34. Fournel S, Aguerre-Guirr M, Huc X, Lenfant F, Alam A, Toubert A, Bensoussan A, Le Bouteiller A: Soluble HLA-G1 triggers CD95/CD95 ligand mediated apoptosis in activated CD8+ cells by interacting with CD8. J Immunol 2000, 164:6100–6104
35. Saverino D, Fabbi M, Ghiotto F, Merlo A, Bruno S, Zarcone D, Tenca C, Tiso M, Santoro G, Anastasi G, Cosman D, Grossi CE, Ciccone E: The CD85/LIR-1/ILT2 inhibitory receptor is expressed by all human T lymphocytes and down-regulates their functions. J Immunol. 2000, 165:3742–3755